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EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/002,631	GRAFF ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *114-144* is/are pending in the application.

4a) Of the above claim(s) *129-134* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *114-128 and 135-144* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 114-128 and 135-144) in the reply filed on November 3, 2003 is acknowledged. The traversal is based on the following ground(s):

1. The identification of the "candidate eukaryotic nucleic acid that encodes a polypeptide" includes the analysis of the function of the polypeptide because the secretion of the polypeptide is one criteria used for identification of the nucleic acid, and this does not preclude one from an additional related step of analyzing the function of the polypeptide (see for example page 4 of Applicant's traversal).

2. An analysis of whether the candidate is associated with a disease condition is also encompassed by the identification of a polypeptide as comprising a signal sequence (see for example page 4 of Applicant's traversal).

This is not found persuasive because of the following reasons:

1. The identification of the function of a polypeptide is not included within the method of identifying a signal sequence within the polypeptide. This is obvious from the fact that not all secreted polypeptides have the same function. For example, as set forth in the instant specification in paragraphs [0005] and [0007], a secreted polypeptide may be involved in cell adhesion, cell migration and/or cell metastasis, and may function as a hormone, enzyme, cell differentiation factor, cytotoxic peptide, neuropeptide, etc. Each of these polypeptides has a different function, therefore simply identifying a polypeptide as having a signal or transmembrane sequence does not necessarily include identifying the function of the protein.

Indeed, in order to identify the function of the polypeptide identified as having a signal sequence, one would have to perform additional unrelated steps to discern the function of the polypeptide. While Applicant is not precluded from performing additional method steps, it is these additional and distinct method steps that make the inventions unrelated (as clearly set forth in the restriction requirement), because a method that identifies a protein as having a signal sequence does not necessarily read on a method of identifying the function of the protein (for the reasons set forth above). The fact of the matter is that identifying a protein as having a signal sequence does not identify the biological function of that polypeptide, therefore the methods are not inclusive of each other.

2. Similar to the rationale regarding why identifying the function of a polypeptide is not analogous to identifying a protein as having a transmembrane sequence, the correlation of a disease condition with a protein requires additional method steps that are not encompassed by method steps for the identification of a transmembrane sequence in a protein. Again, it is evident from the instant specification that many functionally distinct disease conditions are associated with secreted proteins (see for example paragraph [0031]). Simply identifying that one sequence has a transmembrane sequence does not necessarily identify what disease the protein may (or may not) be associated with, because it does not even determine that natural function of the protein (see above). In order to associate the protein with a disease, one would have to perform additional method steps to (a) identify the function of the protein and (b) see if that function is associated with a particular disease. Again, it is these additional and distinct method steps that make the inventions unrelated (as clearly set forth in the restriction requirement).

The requirement is still deemed proper and is therefore made FINAL.

It is noted that in the decision for the petition to make this application special, Applicant was required to make an election without traverse or lose the status of the application as special (see the attached copy of the Petition decision, last line of the third full paragraph). Because the election was traversed, the special status of the application as special is considered void.

Claims 114-144 are pending in the instant application. Claims 129-134 are withdrawn from consideration as being drawn to a non-elected invention. Claims 114-128 and 135-144 are under examination in the instant application.

Miscellaneous

Applicant's declaration under 37 CFR § 1.131, filed July 28, 2003, is acknowledged.

Priority

Applicant's claim for domestic priority to US Application 60/300,309 under 35 U.S.C. 119(e) is acknowledged.

Information Disclosure Statement

The information disclosure statement filed April 22, 2004 has been considered, and a signed and initialed copy of the form PTO-1449 has been attached to this Office Action.

It is noted that Applicant makes reference to an IDS filed on February 3, 2003, relating to references cited in an International Search Report. However, a form PTO-1449 is not present in

the file with this reference, only the International Search Report; an International Search Report cannot be considered as a form PTO-1449. These references have been considered with regard to the patentability of the invention; however, a form PTO-1449 citing the references is necessary in order to provide a physical record that the references were considered, should the application go to issue. The Office will officially make the references of record upon the provision of an acceptable format (i.e., a form PTO-1449).

It is noted that Applicant discusses several references in the paper filed April 9, 2002, discussing at length the relevance of the references to the instant application. However, there is no reference to an enclosed form PTO-1449, nor does one appear with that paper. Although the references have been considered with regard to the patentability of the invention, a form PTO-1449 citing the references is necessary in order to provide a physical record that the references were considered, should the application go to issue. The Office will officially make the references of record upon the provision of an acceptable format (i.e., a form PTO-1449).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 114-128 and 135-144 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 114 and 115 (and all dependent claims) are rejected under 35 USC 112, second paragraph, as being indefinite for failing to recite a positive process step that refers back to the

preamble of the claim. In order for the claimed method to be definite in terms of the metes and bounds of the invention, the claim must recite a method step that provides for the result of the methods as claimed. In the instant case, the claims are directed to a method of "identifying a candidate eukaryotic nucleic acid that encodes a polypeptide which comprises a signal sequence and/or transmembrane sequence," but the claim does not contain a method step whereby the sequence is identified. As such, the claim is open ended, and the claim lacks definitive metes and bounds. It would be remedial to indicate a method step such as "thereby identifying a candidate eukaryotic nucleic acid that encodes a polypeptide which comprises a signal sequence and/or transmembrane sequence."

Claims 114 and 115 (and all dependent claims) rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the utilization of a nucleic acid construct that expresses a marker gene that is expressed only if an intact signal sequence region is present in the construct, and wherein said construct comprises a mutation in the signal sequence region. The specification clearly indicates that such a construct is used for the screening assay of the invention (see for example paragraph [0053] on page 16 of the instant specification). Without the description of such a construct, it is unclear how the expression of the candidate eukaryotic relates to the functionality of the marker gene. In other words, there is no nexus between the function of the marker gene and the ability of the candidate eukaryotic nucleic acid to function as a signal/transmembrane sequence without a clear presentation that the candidate eukaryotic nucleic acid functionally complements the mutation in the signal sequence region of the marker gene.

Claim 115 (and its dependent claims) recites the limitation "comprises a signal sequence *and/or* a transmembrane sequence" (emphasis added) in the last line of the claim. There is insufficient antecedent basis for this limitation in the claim because the preamble indicates that the sequence "comprises a signal sequence *and* a transmembrane sequence" (emphasis added). The recitation of "and/or" in the last line of the claim broadens the scope with regard to its presumed antecedent basis in the preamble of the claim, allowing the sequence to be both or either a signal sequence and a transmembrane sequence, whereas the preamble only allows for it to be both. It would be remedial to indicate "and/or" in the preamble of the claim.

Claim 139 is rejected under 35 USC 112, second paragraph, as being indefinite for failing to recite a proper Markush group. In order for the claims to be definite, they must recite the proper Markush language, wherein the members of the Markush group are "selected from the group consisting of", followed by the listing of the members of the group. In addition, the conjunction "and" must follow the penultimate member of the group. In the instant case, the group is improper because it is unclear what the group is that is being selected from. For instance, it is unclear if two markers are being selected simultaneously (e.g., a fluorescent protein and an antibiotic resistance gene) versus a single marker gene that is a toxin resistance gene, or if the selection can be made from any one of the members set forth in the group. It would be remedial to remove the initial conjunction "and" and replace the second conjunction "or" with "and" to bring the claim into proper Markush format.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 114-118, 123, 126-128, 135-138 and 141-144 are rejected under 35 U.S.C. 102(b) as being anticipated by McCarthy *et al.* (US 5,952,171; see entire document; henceforth McCarthy).

It is noted that this rejection is predicated on the fact that there is no limitation set forth in the instantly rejected claims that excludes performing the selection step in a cell other than the originally contacted bacterial cell. A careful reading of the rejected claims indicates that the method simply requires that the nucleic acid being tested is present in a bacterial cell at some time prior to the selection step.

McCarthy teaches a method for identifying a cDNA nucleic acid encoding a mammalian (eukaryotic) signal sequence by ligating the sequence to a DNA encoding a mutant version of alkaline phosphatase that lacks its native signal sequence (see for example the Abstract and column 5, lines 14-57). The hybrid sequence is transformed into a bacterial cell, isolated, and retransformed into mammalian cells that lack alkaline phosphatase (see for example the Abstract and column 5, lines 14-57). The supernatant collected from the medium containing the mammalian cells is then tested for alkaline phosphatase activity (see for example the Abstract, column 5, lines 14-57 and column 8, lines 30-34), which will only be present if the mammalian sequence comprises a signal sequence that functionally compensates the native alkaline phosphatase signal sequence. In certain embodiments, the bacterial cell that is initially contacted

with the hybrid nucleic acid is a gram-negative *E. coli* cell (see for example column 7, lines 5-13). The candidate eukaryotic sequences are generated as a cDNA library from a human fetal brain tissue (see for example column 6, lines 27-28), meeting the limitations of vertebrate, mammalian and human for the origin of the nucleic acid. The cDNA sequences are cloned via a restriction site into a cloning site of the ptrAP3 expression vector, creating a fusion between the candidate sequence and the marker gene (see for example column 7, lines 9-11). The alkaline phosphatase is a measurable marker gene that can be detected by phospho-imaging (see for example column 8, lines 30-39). The polynucleotides encoding a signal sequence can then be isolated and sequenced following the selection process (see for example column 5, lines 14-57).

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 114-128, 135-138 and 141-144 are rejected under 35 U.S.C. 102(e) as being anticipated by Greener *et al.* (US 2003/0096223; see entire document; henceforth Greener).

Greener teaches a method for the identification of proteins with a signal sequence using a marker sequence, and screening for marker activity in an *E. coli* host cell (see for example paragraphs [0006]-[0011] and [0100]). In one embodiment, the selectable marker used is a cell surface protein that is not present in the host cell, and the polynucleotide being screened is fused to the cell surface protein (see for example paragraph [0026]). In this instance, the cell surface protein is mutated such that it no longer contains a signal sequence (see for example paragraph [0015]), and thus cannot be expressed on the surface of the cell without complementation by the candidate nucleic acid (see for example paragraph [0026]). The expression of the cell surface

protein can then be measured by virtue of its ability to bind to a ligand, such as an antibody (see for example paragraph [0026]), where the activity requires the presence of a signal sequence to reconstitute its direction to the cell surface. In instances where the lamB marker is used, the cells can be tested for the acquisition of a new resistance marker via infection by a virus (see for example paragraph [0049]), thereby allowing the cells to be screened based on their survival in the presence of a compound for which the new resistance marker is required. The candidate polynucleotides that are screened in the invention can be generated from a eukaryotic source (see for example paragraph [0080]). In general, the candidate polynucleotides are in the form of a library, and the library can be generated from any human, mouse or other vertebrate cell line available from the American Type Culture Collection (see for example paragraphs [0089-0092]), of which the MCF7 cell line (ATCC HTB-22) is a member. The candidate polynucleotides are then fused to the marker gene in an expression vector containing all of the necessary elements (including a cloning site with a restriction site for introducing the library polynucleotide into the vector), prior to the transformation and screening in a host cell (see for example paragraphs [0066]-[0076]). The polynucleotides having the capacity to encode a signal sequence can then be isolated and sequenced following the selection process (see for example paragraphs [0106]-[0111]).

Claims 114-118, 123-128 and 135-144 are rejected under 35 U.S.C. 102(e) as being anticipated by Duffner *et al.* (IDS reference; see entire document; henceforth Duffner).

Duffner teaches a method of identifying and/or isolating a gene of interest encoding a signal sequence comprising the following steps: fusing a library clone with a polynucleotide (i.e.,

a marker gene) lacking an operational signal sequence, introducing the fusion into a host cell, screening for the active secretion of the marker, and identifying the library clone which reconstitutes the secretion of the marker (see for example paragraphs [0008]-[0021]). The fusions are generally expressed from an expression vector (see for example paragraphs [0061]-[0064]), wherein the fusion is cloned into a multiple cloning site via the presence of a restriction endonuclease site. Host cells useful in the invention include prokaryotic organisms such as *E. coli* (see for example paragraph [0072]-[0074]). The nucleic acids being screened can originate as DNA or cDNA libraries from any multicellular organism, including human cells (see for example paragraphs [0105]-[0106]). In a specific example, the marker protein that is used is a mutant version on the β-lactamase gene (which confers resistance to ampicillin), wherein the native signal sequence is rendered inoperable (see for example paragraph [0167]). The library closes are fused to this mutant marker gene, and when the library clone encodes for a signal sequence, the marker is secreted out of the host cell where it functions to confer resistance to ampicillin (See for example paragraphs [0110]-[0111]); this marker can be measured/screened, etc. via both an enzymatic and antibiotic resistance process. When a clone is identified that confers resistance in the presence of ampicillin, the clone is then sequenced and identified in accordance with the method (see for example paragraphs [0008]-[0021]).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 119-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duffner as set forth above in the rejections of claims 114 and 115 (as well as claims 116-118, 123-128 and 135-144) in view of Greener as set forth above in the rejection of claims 114-128, 135-138 and 141-144 (which includes the limitations of claims 119-122).

Duffner teaches all of the elements set forth above in the rejection under 35 USC § 102(e). This involves the screening of cDNA libraries obtained from any human cell line. However, Duffner does not specifically teach using cancer cells, specifically breast cancer cells, and more specifically particular breast cancer cell lines such as MCF7, as the source of the nucleic acid to be screened in the library.

Greener teaches a method for screening a library of nucleic acids for the presence of a sequence that encodes a signal sequence, whereby the source of the nucleic acid can be any ATCC cell line. This includes the breast cancer cell line MCF7 (ATCC HTB-22).

It would be obvious to the ordinary skilled artisan to combine the teachings of Duffner and Greener because both teachings involve the identification of library clones from eukaryotic cDNA libraries that encode signal sequences using a prokaryotic host cell for the screening process. The ordinary skilled artisan would be motivated to use the specific libraries set forth by Greener because Duffner clearly contemplates using libraries from any commercially available human cell line. The ordinary skilled artisan would be motivated to use the commercially

available HTB-22 host cell to generate a library because Greener teaches not only that the cell line is commercially available, but also that it is useful for screening for the presence of nucleic acids encoding signal sequences. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when practicing the invention of Duffner with any nucleic acid library generated from any human cell line, which necessarily includes one that originates from the MCF7 breast cancer cell line disclosed by Greener.

Allowable Subject Matter

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Lambertson, Ph.D.
AU 1636

JAMES KETTER
PRIMARY EXAMINER